Conflict of interest The authors declare no competing conflict of interest.

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Health & Medical Informatics

Murakoshi et al., J Health Med Informat 2013, S11
http://dx.doi.org/10.4172/2157-7420.S11-005

Research Article Open Access

The Treatments of Twin-Twin Transfusion Syndrome in Monochorionic Twin Pregnancies by the Fetoscopic Laser Photocoagulation

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Abstract

Aims: Fetoscopic laser surgery has been widely accepted of optimal treatment for Twin-Twin Transfusion Syndrome (TTTS) in monochorionic twin pregnancies. To avoid surgical complication and to improve the outcome, various techniques employed in our institution. The aim of our study is to assess the clinical outcomes of TTTS after laser surgery with combined various techniques.

Methods: We performed 171 cases of fetoscopic laser surgery for TTTS from 2002 to 2011 in our institution. Various techniques employed in our studies to improve the learning of laser surgery and to achieve successful outcome were; (1) A very thorough mapping of vascular anastomoses before and after ablation; (2) Obliteration of arterio-venous anastomoses from donor to recipient should be done first, (3) Trocar assisted technique using gentle indent the trocar withdrawing the scope shortly, to ablate anastomoses easily, (4) A virtual line was drawn by laser at the hemodynamic equator to avoid residual anastomoses, and not to miss small anastomoses.

Results: Laser photocoagulation was performed since 2002 in our institute, compiling 171 cases. Overall survival was 78% with 5% neonatal morbidity. Both twins survived for 64%, and the survival of one twin was 93%. The recurrent TTTS rate was 1%, and the residual vessel rate was 2%.

Conclusion: A successful outcome for fetoscopic laser surgery is achievable and the outcome is improved in severe TTTS cases by these techniques.

Keywords: Twin-twin transfusion syndrome; Fetoscopy; Laser; Amnioreduction; Ultrasonography

Introduction

Fetoscopic laser surgery for severe Twin-Twin Transfusion Syndrome (TTTS) has been conducted since early 1990s in United States and Europe. After the conclusion of Eurofetus in the randomized clinical trial [1], fetoscopic laser surgery has become the standard and optimal treatment for the TTTS condition. Recently, the techniques have been implemented throughout the globe; many institutions have instituted the performance of fetoscopic laser surgery. As with many new procedures, fetoscopic laser surgery has a steep learning curve for a variety of reasons, i.e., challenging placental location, complex and unexpected communicating anastomoses, dividing membrane lifting, residual anastomoses after surgery, or discolored amniotic fluid. The laser surgery has been performed in Japan since 2002, and five laser centers employ the same protocols. More than 700 TTTS cases, 180 cases were treated by laser surgery to date in our institution. The new technical tips to improve the achievement of successful outcome will be introduced and reviewed for laser surgery and our data of perinatal outcome and complication of fetoscopic laser surgery for severe TTTS will be indicated in this article.

Pathophysiology and diagnosis of TTTS

Because of vascular anastomoses between the fetuses, monochorionic twin pregnancies have a high-risk profile compared with dichorionic twin pregnancies. TTTS is one of the major complications resulting from vascular anastomoses and their imbalanced blood distribution in about 5-10% of monochorionic twins. TTTS can be characterized by an imbalanced blood distribution, due to a net flow from one fetus (the donor twin) to the other (the recipient twin) through placental communicating vessels. The donor twin is characterized by a hypodynamic status, manifested by hypovolemia, hypotension, oliguria, oligohydramnios, fetal growth restriction, and renal failure. These processes ultimately result in fetal demise. In contrast, the recipient twin is characterized by a hyperdynamic status, hypervolemia, hypertension, polyuria, polyhydramnios, heart failure, and hydrops fetalis; thus it often also results in a fetal demise. The prognosis for severe early onset TTTS is dismal, with perinatal mortality rates of up to 90% if untreated.

TTTS is defined prenatally by ultrasonography as: a monochorionic diamniotic twin pregnancy; polyuric polyhydramnios in the recipient twin (maximum vertical pocket >8 cm, and large distended bladder) with oliguric oligohydramnios in the donor twin (maximum vertical pocket <2 cm and collapsed or non-visible bladder) simultaneously; and no signs of abnormality due to poly- or oligo-hydramnios. Once the diagnosis of TTTS is made, the severity is classified by Quintero's stage [2] from I to V. Stage III TTTS is sub-classified into two sub-groups defined by whether the donor bladder is visible or non-visible. Sub-classification of Stage III [2,3] is defined as follows: Stage III classical (Doppler studies are critically abnormal in either twin and the bladder of the donor is not visible); and Stage III atypical (Doppler studies are critically abnormal in either twin and the bladder of the donor is still visible).

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Received March 14, 2013; **Accepted** April 18, 2013; **Published** April 24, 2013

Citation: Murakoshi T, Naruse H, Nakayama S, Torii Y (2013) The Treatments of Twin-Twin Transfusion Syndrome in Monochorionic Twin Pregnancies by the Fetoscopic Laser Photocoagulation. J Health Med Informat S11: 005. doi:10.4172/2157-7420.S11-005

Methods and Subjects

Concept of fetoscopic laser surgery for TTTS

Fetoscopic laser surgery of communicating vessels for severe TTTS consists of a few basic principles: in as much as imbalanced blood distribution due to placental vascular anastomoses are thought to be the main cause of TTTS, laser ablation of communicating vessels can eliminate the cause of TTTS; and all anastomoses (AV (Arterio-Venous), AA (Arterio-Arterial), VV (Veno-Venous Anastomoses) can be visualized and ablated by a fetoscopic procedure.

Preparation for fetoscopic laser surgery

Essentially, before attempting the procedure, operators should be knowledgeable of the complex pathophysiology of TTTS and other TTTS-related events such as Twin Anemia Polycythemia Sequence (TAPS), acute feto-fetal hemorrhage after single fetal demise, Selective Intrauterine Growth Restriction (sIUGR) in monochorionic twin, and Twin Reversed Arterial Perfusion (TRAP) sequence. Ultrasound assessment should be conducted and the echocardiographic features of TTTS must be evaluated. The donor twin is characterized by a hypovolemic status of the placenta and circulatory insufficiency. Fetal growth restriction and umbilical arterial Doppler abnormalities are common ultrasound features. Doppler examination reveals a decrease in the end-diastolic velocity of the umbilical artery, especially the absence or reverse end-diastolic velocity in Stage III or IV. Decreased peak systolic velocities of the descending aorta are also common. Coarctation of the aorta in the donor or smaller fetus in a monochorionic twin pregnancy has been reported and, based on the hemodynamic theory, decreased blood flow into the donor or smaller twin might increase the risk of a coarctation of the aorta [4]. Most recipient fetuses develop cardiac dysfunction complicated by cardiomegaly, tricuspid and mitral valve regurgitation, ventricular hypertrophy, increased reverse flow in the inferior vena cava, and pulmonary stenosis; they also develop reverse flow of the ductus venosus and pulsatile flow in the umbilical vein [5,6]. Typically, mild cardiomegaly and increased reverse flow in the inferior vena cava occurs first; moreover, right ventricle compromise occurs earlier than left ventricle. Congestive heart failure and hydrops fetalis in the recipient may originate from chronic volume and pressure overload of the right ventricle. These conditions lead to cardiomegaly and atrio-ventricular valve regurgitation. Occasionally, some cases of a severely affected recipient can develop into acquired pulmonary stenosis/atresia with an intact ventricular septum [5,7].

Additionally, the operator should be trained to identify and characterize the vascular anastomoses of the monochorionic placenta. Placental dye injection examination [8,9] of the monochorionic placenta should be an important step before attempting laser surgery (Figure 1). All vessels on the placental surface can be precisely differentiated by fetoscopic inspection; arteries principally cross over veins and the color of arteries is dark blue due to deoxygenated blood, whereas veins appear bright red due to oxygenated blood from the placenta. AA and VV anastomoses are directly linked artery-to-artery or vein-to-vein, and have no terminal ends. While AV anastomosis is not anatomical anastomosis itself, the artery (feeding artery) comes from a fetus to cotyledon, and goes to the other fetus as drainage vein. It is called an AV anastomosis. Occasionally, three or four vessels cotyledons are seen, in which three or four types of different vessels are in to same cotyledon. AA anastomoses are theoretically complex and bidirectional transfusion depends on the location of the hemodynamic equator and branch of artery. This mechanism can provide AA anastomoses as

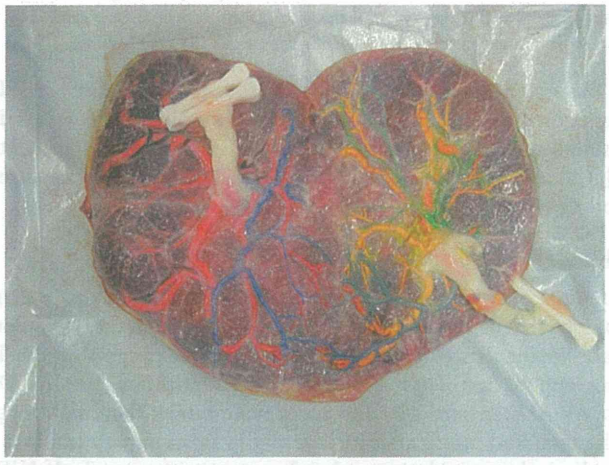

Figure 1: Dye injections into vessels of monochorionic placenta after delivery.

functional AV behavior for both directions [10]. Blue or green dye was injected into the artery, and red or yellow dye into the vein.

Setting and performance of fetoscopic laser surgery (Procedural steps)

Epidural anesthesia or local anesthesia with maternal conscious sedation can be chosen for fetoscopic laser surgery. In our first 36 cases, general anesthesia was chosen; this option was similar to that of other institutions in the early period of fetoscopic laser surgery because immobility of the fetuses especially in the recipient fetus; however, after operator skills improved, epidural or local anesthesia were chosen because they were less invasive for the mother and could decrease maternal complications [11]. After adequate anesthesia was achieved, a 3.8 mm trocar (Richard Wolf, Vernon Hills, IL, USA) was inserted into the recipient amniotic sac with ultrasonographic guidance. Appropriate fetoscopes (i.e., Richard Wolf angled-view endoscope, 2.8 mm diameter, 30 cm length; 25 degree (RW-8930.402), 30 degree (RW-8930.422), 70 degree (RW-8660.412), operative 12 degree with working channel for 5 Fr instruments (RW-8746.401); and a 2 mm diameter, 26 cm, 0 degree rigid telescope (K26008AA, Karl Storz, Tuttlingen, Germany) with sheath (K11630KH)) were selected according to the placental and fetal location. All communicating vessels were initially mapped and then ablated by Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG) laser (Surgical Laser Technology, Montgomery, PA); this was conducted via the non-contact method with fetoscopic guidance. Laser fibers were inserted into the operating channel of the fetoscope and the laser power was usually set from 15 to 40 watts for Nd:YAG (1,064 nm) laser. Re-examination and re-lasering of anastomoses with mapping was then done; subsequently, the hemodynamic equator was drawn by laser. Finally, amnio drainage was done if indicated.

Mapping system

During the procedure, placental vessel mapping helps the operator to identify and orient the direction and location the anastomoses. Before laser ablation, a very thorough mapping of vascular anastomoses must be done by the operator and navigator. Each vascular anastomosis was labeled as AV-DR, AV-RD, AA, or VV (for example, AV-DR represented an arterio-venous anastomosis from donor to recipient); the navigator records this information as figures or comments. During the laser ablation, the operator eliminates each anastomosis by referring to the mapping system. After ablation, reevaluation of all placental

anastomoses should be done. Additionally, by using the mapping system before ablation, we can choose an appropriate sequence for the ablations.

This system also has the potential to reduce the incidence of residual anastomoses and recurrence of TTTS. A low incidence of residual anastomoses and recurrence of TTTS was reported by Cincotta et al. [12], Chmait et al. [13] and our series [3]; all three studies employed a mapping system.

Sequential order

Quintero et al. [14] and Nakata et al. [15] proposed the new technique that all anastomoses should be ablated in a specific order to reduce the incidence of a fetal demise after laser surgery, especially a donor with the loss of or reversed umbilical arterial flow: first, AV-DRs; then, AV-RDs. In particular, the donor twin with an abnormal Doppler of the umbilical artery appears logically to be more vulnerable to an acute hemodynamic change such as hypotension or anemia. If AVRDs are obliterated first, inter twin transfusion from donor to recipient occurs; thus, the donor twin develops increased hypotension and anemia followed by fetal demise. Sequential laser ablation of anastomoses and elimination of the AVDRs prior to the AVRDs could result in improved blood pressure of the donor via an intraoperative inter twin transfusion, rescue as well as stabilization of the hemodynamics of the donor. It is currently controversial whether arterio-arterial and veno-venous anastomoses should ablated first, prior to AV anastomoses, or last; however, an AVDR first policy could reduce fetal demise after laser surgery especially in donors with abnormal Doppler [14,15]. The US Fetus Consortium is currently undergoing a randomized control trial to compare outcomes between the standard laser approach and the sequential laser approach.

Trocar assisted techniques in anterior placenta

An anterior placenta is the most difficult settings for FLP, i.e., it becomes quite difficult to confirm the anastomoses and to ablate the vessels, because of the tangential angle of target vessels and fetoscope alignment. Quintero et al. [16] originally proposed the technique of trocar-assisted selective laser photocoagulation. The rigid trocar is gently inserted behind the anteriorly located placenta by withdrawing the scope within the trocar a short distance, where the angle is adequate to ablate the vessels, as it is perpendicular by the technique, pushing the trocar close to the target vessel. At this point, the anastomoses can be easily ablated because the target vessel and fetoscope are perpendicular rather than tangential. The trocar-assisted technique has three benefits: (1) It allows perpendicular rather than tangential alignment of the target vessels; (2) Reduction of the blood flow in large communicating vessels (Figure 2). The pressure exerted by the trocar reduces the flow and allows for ablation with less laser energy; and (3) the technique is possible to avoid inadvertent injury to the fetus and dividing membrane for safe ablation of the target vessels. One type of fetoscope can be used without the trocar, i.e., an appropriate fetoscope can be selected, i.e., 0 degree, 30 degree, or 70 degree is selected for an anterior placenta. Furthermore, both Richard Wolf and Karl Storz instruments fit a 3.8 mm cannula.

The rigid trocar is gently inserted behind the anteriorly located placenta withdrawing the fetoscope in the trocar for a short distance. The perpendicular angle is adequate to ablate the vessels after the trocar assisted technique.

Line drawing methods

A virtual line should be drawn with the laser at the hemodynamic equator, but not the membrane equator, to avoid residual anastomoses (Figure 2). The technique is also reported as the Solomon technique; which is a trial currently ongoing to test this method in Europe (www.trialregister.nl, trial ID: NTR1245). Small anastomoses are not missed by the virtual line method. First, selective laser ablation is performed to avoid residual anastomoses at each vascular end of anastomotic vessels and to avoid residual anastomoses. Second, the technique constructs a dotted line with the laser; and finally forms a virtual line with the laser along the hemodynamic equator (Figure 3). The technique draws the doted line with laser ablation along with the hemodynamic equator, creating the dichorionized placenta.

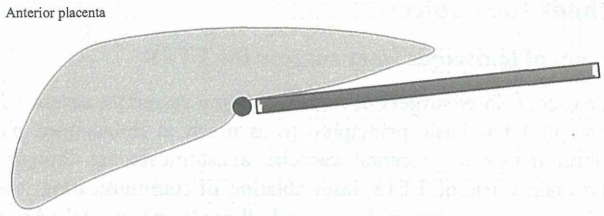

Figure 2: Trocar assisted technique.

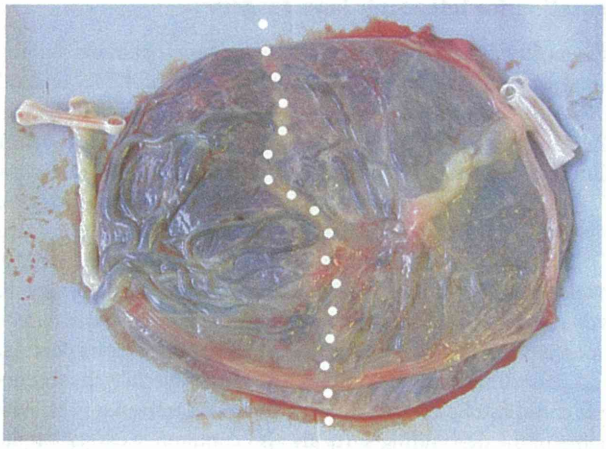

Figure 3: Line drawing method.

TTTS patients

One hundred and fifty two Japanese women whose pregnancy was complicated by severe TTTS before 26 weeks of gestation underwent fetoscopic laser surgery in our institution in the years from 2002 to 2011. All patients were delivered and their infants were followed-up for at least six months. TTTS was diagnosed in monochorionic twin pregnancies based on standard ultrasound criteria: polyhydramnios and oligohydramnios with the deepest vertical amniotic pocket measuring at least 8.0 cm in the recipient and at most 2.0 cm in the donor. All patients met the following criteria for laser surgery: gestational age less than 26 weeks; and Quintero's stage classification was I to IV. The laser procedure for placental communicating vessels was based on a previously reported method [3] with additional techniques described above if indicated: mapping system; sequential order of AV-DR first policy if possible; using a trocar of appropriate diameter for the fetoscope; employing trocar-assisted technique and laser line drawing methodology. Patient baseline and surgical characteristics are presented in (Table 1). Sixty eight percent of the patients were stage III (54%) and IV (14%), and 51% of the patients had an anterior placenta.

Maternal Age (year)	30 (15–42)
Gestational age at surgery (weeks)	21 (16–25)
Location of placenta	
Anterior	87 (51%)
Posterior	84 (49%)
Quintero stage	
Stage I	19 (11%)
Stage II	36 (21%)
Stage III	92 (54%)
atypical	31
classical	61
Stage IV	24(14%)
Complete surgery	170 (99%)
Anesthesia	
General	36 (21%)
Epidural	135 (79%)
Operation time (minutes)	58 (24–158)

Data are shown as median (range) or number (%)

Table 1: Baseline and surgical characteristics (n=171).

Gestational age at delivery (weeks)	33 (19–40)
Miscarriage (delivery<22 weeks)	6 (3.5%)
Recurrent TTTS	1 (0.6%)
TAPS	2 (1.2%)
Residual anastomoses	4 (2.4%)
Overall survival (n=342)	267/342 (78%)
Neurological sequels (n=267)	13/267 (4.9%)
2 survivors	110 (64%)
1 survivor	49 (29%)
0 survivor	12 (7%)
At least 1 survivor	159 (93%)

Data are shown as median (range) or number (%)

Table 2: Pregnancy outcome and survival rates (n=171).

Stage	**I n=19**	**II n=36**	**III atypical n=31**	**III classical n=61**	**IV n=24**
2 survivors	13 (69%)	26 (72%)	14 (45%)	42 (69%)	15 (67%)
1 survivor	5 (26%)	6 (17%)	15 (48%)	14 (23%)	9 (33%)
0 survivor	1 (5%)	4 (11%)	2 (7%)	5 (8%)	0 (0%)
At least 1 survivor	18 (95%)	32 (89%)	29 (93%)	56 (92%)	24 (100%)
Overall survival	31/38 (82%)	58/72 (81%)	43/62 (69%)	98/122 (80%)	39/48 (81%)
Neurological sequels	1/31 (3.2%)	4/58 (6.9%)	3/43 (6.9%)	2/98 (2.0%)	3/39 (7.7%)

Data are shown as number (%)

Table 3: Perinatal outcome according to Quintero stage.

Results

We completed laser surgery on 99% of the patients. The median surgical time was 58 minutes; however, surgical time was counted from the insertion of the trocar to amino drainage with the following intervening steps: fetoscopic inspection, mapping, and laser ablation. (Tables 2 and 3) present the perinatal outcomes. The overall survival rate was 78%; and 4.9% of the cases had neurological sequels including periventricular leukomalacia, intraventricular hemorrhage grade 3 and 4, and cerebral palsy. At six months after delivery: in 64% of the cases, twins survived; in 29% of the cases, one twin survived; and in 93% of the cases at least one twin survived. The Quintero stage did not worsen in any of the survivors; however, stage III atypical, which was defined as abnormal Doppler flow with visible donor bladder, had a decreased survival rate especially in 2 survivors.

	Ville et al. [19] n=132	Hetcher et al. [17] n=73	Hetcher et al. [20] n=200	Quintero et al. [10,18] n=95	Senat et al. [1] n=72	Huber et al. [22] n=200	Middledorp *et al.* 2007 n=100	Cincotta et al. [12] n=100	Chmait et al. [23] n=682	Present study 2012 n=171
Median gestational age at delivery (weeks)	-	33	34	32	33	34	33	31	33	33
Perinatal survival (%)	55	61	-	64	56	72	70	76	79	78
Neurological sequels (%)	4	6	6	4	7	-	-	3		5
2 survivors (%)	36	42	50	44	36	60	58	66	72	64
1 survivor (%)	38	37	30	38	38	24	23	19	18	29
0 survivor (%)	26	21	20	17	26	17	19	15	10	7
At least 1 survivor	74	79	80	82	74	84	81	85	90	93

Table 4: Comparison of perinatal outcomes in published series.

Discussion

Table 4 presents the perinatal outcomes in published series including early series of pioneer operators [1,17-20] and published data [12,21-24] from the conclusion of the Eurofetus trial comparing to the present study. Early series reported approximately a 60% overall survival rate, a 5% neurological complication rate; and a 40% survival rate of both twins. Middledorp et al. [21], Cincotta et al. [12], Huber et al. [22], and Chmait et al. [23]describe improved perinatal outcomes: >70% overall survival, 58-69% with two survivors and; >80% with at least one survivor. Hecher et al. [20] and Huber et al. [22] reported the data from their 400 consecutive case series divided into two groups: the first 200 and last 20. As their experience increased, they reported an increasing overall survival rate, especially for cases of two survivors. In our series, the overall perinatal survival for at least six months was 78%; the neurological complication rate was 5%; the rate for both twins surviving was 64%; and at least one twin survived in 93% of the cases. These data appear favorable and are comparable to that of the latest 200 case series of Huber et al. [22]. We attribute our favorable results to mapping, trocar assisted techniques, selection of the appropriate fetoscope, sequential order ablation, and the laser line drawing method. Neurological sequels were periventricular leukomalasia, interaventricular hemorrhage grade III and IV and cerebral palsy.

Conclusion

In view of our experience regarding the management of TTTS, comprehensive techniques including preparation of various new devices, selection of instruments, and advanced laser ablation techniques have contributed to the progress of fetoscopic laser surgery for TTTS in monochorionic twins.

Acknowledgement

Authors express sincere gratitude to the members of Seirei Hamamatsu general hospital, particularly for the supports of Drs. M Matsushita, T Shinno, T Arakaki, and T Mishima.

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Citation: Murakoshi T, Naruse H, Nakayama S, Torii Y (2013) The Treatments of Twin-Twin Transfusion Syndrome in Monochorionic Twin Pregnancies by the Fetoscopic Laser Photocoagulation. J Health Med Informat S11: 005. doi:10.4172/2157-7420.S11-005

This article was originally published in a special issue, **Global Progresses in the Perinatal Medicine** handled by Editor(s). Dr. Kazuo Maeda, Kyushu University Medical School, Japan

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2014) ∞, ∞–∞ doi: 10.1111/ped.12233

Original Article

Incidence and prediction of outcome in hypoxic–ischemic encephalopathy in Japan

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Abstract ***Background***: Hypoxic–ischemic encephalopathy (HIE) is one of the most critical pathologic conditions in neonatal medicine due to the potential for neurological deficits in later life. We investigated the incidence of term infants with moderate or severe HIE in Japan and identified prognostic risk factors for poor outcome in HIE.

Methods: Data on 227 infants diagnosed with moderate or severe HIE and born between January and December 2008 were collected via nationwide surveys from 263 responding hospitals. Using logistic regression, we examined the relationship between maternal, antepartum, intrapartum, and neonatal risk factors and clinical outcome at 18 months following birth.

Results: In Japan, the incidence of moderate or severe HIE was 0.37 per 1000 term live births. Outborn births, low Apgar score at 5 min, use of epinephrine, and low cord blood pH were intrapartum factors significantly associated with neurodevelopmental delay and death at 18 months. Serum lactate, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase (all, $P < 0.001$) and creatine kinase ($P = 0.002$) were significantly higher in infants with poor outcome compared to those with favorable outcomes. Abnormal brain magnetic resonance imaging (MRI), an important prognostic factor, was significantly associated with poor outcome (odds ratio, 11.57; 95% confidence interval: 5.66–23.64; $P < 0.001$).

Conclusions: Risk factors predicting poor outcome in HIE include outborn birth, low Apgar score at 5 min, use of epinephrine, laboratory abnormalities, and abnormal MRI findings.

Key words hypoxic–ischemic encephalopathy, magnetic resonance imaging, neurodevelopmental outcome, risk factor.

Hypoxic–ischemic encephalopathy (HIE) is one of the most critical pathologic conditions in neonatal medicine. Infants with HIE suffer neurological sequelae in later life.[1–4] Some studies have reported predictive factors for neurodevelopmental outcome in infants with HIE.[5–7] Electroencephalography (EEG), magnetic resonance imaging (MRI), and laboratory data at birth are useful tools for predicting outcome based on neonatal risk factors. Whereas maternal and antenatal factors may foretell the development of HIE, these variables do not predict mortality or neurodevelopmental outcome.[8–10]

Neonatal encephalopathy (NE) refers to neurological abnormalities manifesting in the neonatal period and may be caused by multiple variables, among which, HIE is a key contributing factor. The incidence of NE has been reported in several studies.[8,11,12] The incidence of NE is 1–4 per 1000 live births,[8,11]

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Received 10 September 2013; revised 27 September 2013; accepted 4 October 2013.

but there are few reports of the incidence of HIE.[12–14] This may be due to the fact that establishing a diagnosis of HIE may be challenging because infants may present with non-specific symptoms and HIE is not always caused by a sentinel event.[4,15] Further, in some cases, an obvious hypoxic–ischemic event may have not been apparent during the intrapartum period or immediately after birth.[15] Because of the diagnostic difficulty, neonatologists and obstetricians are not always able to recognize brain insult in infants who suffer partial asphyxia at birth. Therefore, the incidence of HIE might be underestimated.

Accordingly, the aim of this study was to describe the incidence of HIE in term babies in Japan. Additionally, we investigated the risk factors for neurological sequelae and death.

Methods

This retrospective survey study was approved by the ethics committees of the National Center for Child Health and Development (approval number, 575; date of approval, 5 June 2012). We conducted a nationwide cohort study to retrospectively collect data on term infants with HIE who were born between January and December 2008. The survey was designed to include term infants (≥37 weeks) who had moderate or severe HIE caused by obvious perinatal asphyxia. Term infants without obvious perinatal asphyxia were also included if they demonstrated any of the following during the first 72 h after birth: abnormal consciousness, difficulty maintaining respiration, abnormal tone and reflexes, or neonatal seizures. We excluded infants with acute encephalopathy resulting from causes other than hypoxic–ischemic events, that is, congenital abnormality, chromosomal abnormality, electrolyte abnormality, hypoglycemia, metabolic disease, neuromuscular disease, neurocutaneous syndrome, idiopathic stroke, intracranial hemorrhage, and central nervous infection.

Questionnaires were sent to 290 hospitals associated with the authorized educational facilities of the Japanese Society of Maternal Perinatal Medicine. Of the 290 hospitals, 263 responded, resulting in a response rate of 90.7%. Two hundred and ninety-four infants fulfilled the inclusion criteria. Due to the nature of the survey, patient data were not collected in entirety, and 67 cases had missing outcomes data for the 18 month period following birth. Incidence was estimated based on the total number of eligible subjects ($n = 294$), whereas risk factors were analyzed using data on 227 infants.

The questionnaire consisted of items concerning maternal, ante/intrapartum and neonatal factors. Maternal factors included age (≥35 or <35 years), gravidity, parity, fertility treatment, underlying disease, and medication (with the exception of tocolysis). Ante/intra-partum factors consisted of plurality, hospital of delivery, mode of delivery, induced delivery, instrumental delivery (forceps and/or vacuum delivery), meconium staining, umbilical abnormalities, and placental abnormalities. Fetal heart rate abnormalities included non-reassuring fetal status, bradycardia, deceleration, and loss of or decrease in variability. Fetal heart rate monitoring was evaluated according to the modified definition established by the Japan Society of Obstetrics and Gynecology.

Neonatal factors included gender, gestational age, birthweight, fetal growth, Apgar score (at 1 min and 5 min), and resuscitation. Blood gas analysis of cord blood and the patient's blood as well as the results of blood gas tests performed during admission to the neonatal intensive care unit (NICU) were evaluated.

Brain MRI performed during hospitalization was also reviewed. Decisions regarding whether to perform MRI, technical specifications (such as T1/T2 weighting and image sections), and the timing of imaging were determined by individual clinicians and were based on institutional policy. Abnormal findings included bilateral basal ganglia thalamic lesions, parasagittal injury, subcortical leukomalacia, multicystic encephalomalacia, periventricular leukomalacia, and intracranial hemorrhage.

Neurodevelopmental outcomes were evaluated at age 18 months by the attending physician using neurodevelopmental assessment tools and/or via medical interviews and physical examination. The primary endpoint of this study was outcome at 18 months. Poor outcome was defined as neurodevelopmental delay or death occurring within the first 18 months following birth.

Statistical analysis

In Japan, 1 027 890 term infants were born in 2008; at the time of the survey in 2012, there were a total of 2765 NICU beds. The incidence of HIE among term neonates was calculated based on these data. Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA) and included the chi-squared test, Fisher's exact test for categorical variables, and logistic regression. The main outcome measures were expressed as odds ratios (OR) and the respective 95% confidence intervals (CI). Continuous variables, such as maternal age, gestational age, birthweight and laboratory data, are reported as median and interquartile range (IQR). $P < 0.05$ was considered to be statistically significant.

Results

The median maternal age was 31 years (IQR, 28–35 years), gestational age was 36.6 weeks (IQR, 38.4–40.6 weeks), and birthweight was 2957 g (IQR, 2640–3253 g). Boys comprised 59.5% (135/227) of the study sample; 72 (24.5%) infants were inborn.

Incidence

In 2012, the number of NICU beds in Japan totaled 2765. Among the 263 hospitals responding to the questionnaire, the total number of NICU beds was 2138, which represented 77.3% (2138/2765) of all NICU beds in Japan. Based on the 294 infants meeting the inclusion criteria, the number of infants with moderate or severe HIE in 2008 was projected to be 380 (294/0.773). In 2008, 1 027 890 term infants were born in Japan. Therefore, the birth incidence of moderate or severe HIE was approximately 0.37 per 1000 term live births.

Risk factors for poor outcome

Table 1 lists the potential maternal risk factors for poor outcome. Of these, maternal age (≥35 years), gravidity, parity, fertility

Table 1 Maternal factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Maternal age (years)				
<35	61 (68.5)	94 (74.0)	1	
≥35	28 (31.5)	33 (26.0)	0.76 (0.342–1.39)	0.379
Gravida				
0	55 (61.1)	64 (51.2)	1	
≥1	35 (38.9)	61 (48.8)	1.50 (0.86–2.60)	0.149
Parity				
0	64 (72.7)	82 (65.1)	1	
≥1	24 (27.3)	44 (34.9)	1.43 (0.79–2.59)	0.237
Fertility treatment				
No	75 (90.4)	110 (92.4)	1	
Yes	8 (9.4)	9 (7.6)	0.77 (0.28–2.08)	0.601
Underlying diseases				
No	70 (78.7)	111 (86.0)	1	
Yes	19 (21.3)	18 (14.0)	0.60 (0.29–1.22)	0.153
Maternal medications				
No	82 (90.1)	118 (90.8)	1	
Yes	9 (9.9)	12 (9.2)	0.93 (0.37–2.30)	0.869

CI, confidence interval; OR, odds ratio.

treatment, maternal underlying disease, and maternal medication were not associated with poor outcome. Of the potential antepartum risk factors (Table 2), multiple conceptions did not portend an unfavorable outcome, but outborn birth was associated with a twofold increase in the odds of a poor outcome (OR, 2.07; 95%CI: 1.17–3.36). Mode of delivery, induced labor, and instrumental delivery were not associated with poor outcome, nor were umbilical and placental abnormalities. Fetal heart rate patterns were not associated with neurodevelopmental outcome in infants with HIE (Table 3).

Table 2 Intrapartum factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Plurality				
Singleton	92 (100)	133 (99.3)		
Twins	0 (0)	1 (0.7)	NA	0.406
Hospital of delivery				
Inborn	38 (41.3)	34 (25.4)	1	
Outborn	54 (58.7)	100 (74.6)	2.07 (1.17–3.66)	0.012
Mode of delivery				
Transvaginal	47 (52.2)	70 (56.0)	1	
Caesarean section	43 (47.8)	55 (44.0)	0.85 (0.50–1.48)	0.583
Labor				
Spontaneous	42 (60.9)	63 (63.6)	1	
Induced	27 (39.1)	36 (36.4)	0.89 (0.47–1.67)	0.716
Instrumental delivery				
No	60 (72.3)	82 (73.9)	1	
Yes	23 (27.7)	29 (26.1)	0.92 (0.47–1.75)	0.805
Meconium stain				
No	48 (53.9)	69 (60.5)	1	
Yes	41 (46.1)	45 (39.5)	0.76 (0.44–1.34)	0.346
Umbilical abnormalities				
No	72 (87.8)	88 (80.0)	1	
Yes	10 (12.2)	22 (20.0)	1.80 (0.80–4.05)	0.151
Placental abnormalities				
No	52 (67.5)	72 (69.9)	1	
Yes	25 (32.5)	31 (30.1)	0.90(0.47–1.69)	0.734
Abruptio placentae				
No	54 (70.1)	78 (75.7)	1	
Yes	23 (29.9)	25 (24.3)	0.75 (0.39–1.46)	0.401

CI, confidence interval; NA, not available; OR, odds ratio.

Table 3 Fetal heart rate monitoring

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Non-reassuring fetal status				
No	13 (16.3)	11 (10.3)	1	
Yes	67 (83.8)	96 (89.7)	1.69 (0.72–4.01)	0.227
Bradycardia				
No	52 (65.0)	59 (55.1)	1	
Yes	28 (35.0)	48 (44.9)	1.51 (0.83–2.74)	0.714
Deceleration				
No	13 (28.9)	11 (19.6)	1	
Yes	32 (71.1)	45 (80.4)	1.66 (0.66–4.18)	0.278
Loss/decrease in variability				
No	74 (92.5)	99 (92.5)	1	
Yes	6 (7.5)	8 (7.5)	0.99 (0.33–3.00)	0.995

CI, confidence interval; OR, odds ratio.

Female infants had a significantly higher odds for poor outcome compared to male infants (OR, 1.76; 95%CI: 1.01–3.05; $P = 0.004$). Gestational age and birthweight had no association with poor outcome, whereas low Apgar score (<7) at 5 min more than doubled the odds of poor outcome (OR, 2.31; 95%CI: 1.42–5.23; $P = 0.003$). Similarly, use of epinephrine during resuscitation significantly increased the odds of a poor outcome by nearly sevenfold (OR, 6.90; 95%CI: 1.42–33.30; $P = 0.017$; Table 4).

With respect to laboratory indices, pH and base excess (BE) as determined by blood gas analysis at admission were significantly

Table 4 Neonatal factors

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Gender				
Male	62 (67.4)	73 (54.1)	1	
Female	30 (32.6)	62 (45.9)	1.76 (1.01–3.05)	0.044
Gestational age (weeks)				
37	16 (17.4)	18 (13.3)	0.87 (0.38–2.02)	0.754
38	15 (16.3)	30 (22.2)	1.56 (0.70–3.44)	0.275
39	20 (21.7)	33 (24.4)	1.28 (0.61–2.70)	0.511
40	28 (30.4)	36 (26.7)	1	
41	10 (10.9)	16 (11.9)	1.24 (0.49–3.15)	0.645
42	3 (3.3)	2 (1.55)	0.52 (0.08–3.32)	0.488
Birthweight (g)				
<2499	12 (13.0)	19 (14.3)	0.97 (0.42–2.24)	0.947
2500–2999	35 (38.0)	57 (42.9)	1	
3000–3499	30 (32.6)	41 (30.8)	0.84 (0.47–1.58)	0.586
3500–3999	13 (14.1)	12 (9.0)	0.57 (0.23–1.38)	0.211
≥4000	2 (2.2)	4 (3.0)	1.23 (0.21–7.04)	0.818
Centile birthweight				
<10th	10 (11.4)	23 (17.6)	1.60 (0.72–3.60)	0.249
10th–90th	67 (76.1)	96 (73.3)	1	
>90th	11 (12.5)	12 (9.2)	0.76 (0.32–1.83)	0.542
Apgar score at 1 min				
<7	80 (39.4)	123 (60.6)	2.31 (0.90–5.89)	0.074
≥7	12 (60.0)	8 (40.0)	1	
Apgar score at 5 min				
<7	63 (36.2)	111 (63.8)	2.80 (1.416–5.529)	0.003
≥7	27 (30.0)	17 (13.35)	1	
Resuscitation				
None	5 (5.4)	4 (3.0)	1	
Oxygen	5 (5.4)	8 (6.0)	2.00 (0.36–11.24)	0.431
Bagging/intubation	72 (78.3)	75 (56.0)	1.30 (0.34–5.05)	0.702
Chest compression	4 (4.4)	14 (10.4)	4.37 (0.78–24.39)	0.093
Epinephrine	6 (6.5)	33 (24.6)	6.90 (1.42–33.30)	0.017

CI, confidence interval; OR, odds ratio.

Table 5 Laboratory data

	Good outcome Median (IQR)	Poor outcome Median (IQR)	*P*
Cord blood			
pH	6.97 (6.87–7.14)	6.88 (6.69–7.17)	0.044
BE (mmol/L)	−16.4 (−20.3 to −10.6)	18.4 (−25.8 to −12.1)	0.057
On admission			
pH	7.24 (7.14–7.33)	7.18 (6.92–7.30)	0.003
BE (mmol/L)	−9.9 (−15.2 to −3.65)	18.4 (−21.6 to −6.95)	<0.001
Lactate (mmol/L)	9.4 (4.7–15.0)	11.9 (5.8–17.6)	0.086
WBC (/mm^3)	20520 (14393–26525)	21500 (16300–29900)	0.030
CRP (mg/dL)	0.01 (0.00–0.15)	0.02 (0.00–0.20)	0.901
LDH (IU/L)	673 (507–1204)	987 (662–1866)	<0.001
AST (IU/L)	68 (45–150)	126 (67–20)	<0.001
ALT (IU/L)	17 (10–40)	34 (14–81)	<0.001
CK (IU/L)	642 (433–1328)	1022 (538–2603)	0.002

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells.

lower in infants with poor outcome compared to those with favorable outcomes. Conversely, serum lactate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase (CK) were markedly higher in infants with poor outcome compared to infants with good outcome (Table 5).

Infants who had abnormal findings on brain MRI had a significantly higher risk for poor outcome compared to infants with normal MRI findings (Table 6).

Discussion

Incidence

In this study, the incidence of term infants with moderate/severe HIE in Japan was estimated to be approximately 0.37 per 1000 term live births. A few authors have reported the birth incidence of moderate or severe HIE with rates ranging from 0.46 to 1.26 per 1000 live births.[12,14,16] The variation among the reported data may be due primarily to the difficulty in diagnosing HIE. The diagnosis of neonatal HIE is challenging and typically inferred from non-specific signs.[17] Some infants with HIE have failed to exhibit obvious fetal distress, but nevertheless have suffered from neurological abnormalities immediately after birth.[15] In this study, the subjects consisted of infants with neurological abnormalities due to hypoxic–ischemic events, but not other causes, and included all types of HIE.

Neonatal encephalopathy is a heterogeneous syndrome characterized by signs of central nervous system dysfunction in newborn infants. NE occurs as a consequence of intracranial hemorrhage, hypoglycemia, severe hyperbilirubinemia, various metabolic disorders, and intracranial infection, among other disorders. The reported incidence of NE is 3.8 per 1000 term live births in Western Australia[8] and 1.64 per 1000 term live births in France.[12] Because NE may be caused by events other than hypoxic–ischemic events, the incidence of HIE may differ from that of NE.

Risk factors

Whereas several published studies have reported the ante-/intrapartum risk factors for developing NE and/or HIE,[8–10] none has evaluated the relationship between ante-/intrapartum risk factors and outcome in childhood. The present study found that outborn infants had a significantly higher risk of poor outcome. In Japan, approximately 50% of all neonates are delivered in private clinics. Therefore, it is important that medical staff working in facilities lacking organized perinatal centers receive education on neonatal resuscitation.

Fetal heart rate pattern was not associated with neonatal outcome. The reason for this finding may be the poor specificity of cardiotocography.[18] Similarly, fetal heart rate pattern and abnormalities of the placenta and umbilicus were not related with outcome. We speculated that the inability to estimate the severity of placental and umbilical abnormalities due to the retrospective design of the present study may have contributed to this finding.

Low Apgar score is caused by hypoxic–ischemic injury. Apgar scores at 1 min and 5 min reflect the neonate's general condition immediately after birth and are predictive

Table 6 Brain MRI in hospital

	Good outcome *n* (%)	Poor outcome *n* (%)	OR (95%CI)	*P*
Brain MRI				
Normal	54 (63.5)	14 (13.1)	1	
Abnormal	31 (36.5)	93 (86.9)	11.57 (5.66–23.64)	<0.001

CI, confidence interval; OR, odds ratio; MRI, magnetic resonance imaging.

of neurological outcome, respectively. Several authors have reported that low Apgar score at 5 min is a risk factor for serious morbidity and mortality.[19–21] In the present study, Apgar score at 1 min was not associated with poor outcome, but infants with low Apgar score at 5 min had greater risk of poor outcome compared to infants with higher Apgar score at 5 min. This finding was compatible with that reported in previous studies.

In this study, neonatal resuscitation level was predictive of death or neurological sequelae. The incidence of poor outcome in the infants who received epinephrine was significantly higher than in infants who were not given epinephrine. The need for a high level of resuscitation at delivery has been previously cited as a sensitive predictor of subsequent adverse outcome.[13,22] When the need for cardiopulmonary resuscitation coexisted with severe acidemia, an adverse outcome was likely in >90% of cases.[23]

Both cord arterial lactate and pH are measures of acidemia. Fetal arterial lactate measures anaerobic metabolism whereas fetal pH reflects both anaerobic metabolism and acidemia due to increasing fetal carbon dioxide level. LDH is an important biomarker of cellular damage and is commonly designated as an outcome variable in experimental studies of HIE.[24,25] AST, ALT, and CK as well as LDH may reflect cellular damage occurring in conjunction with extensive tissue damage in one or several organs.

Brain MRI is an essential method for establishing prognosis. One systematic review indicated that diffusion weighted and conventional MRI play an important role in prognostic evaluation.[5] MRI findings in HIE infants are heterogeneous.[2,3,15,26,27] In term neonates with brain injury, the specific regional distribution of injury was associated with different durations and severities of ischemia. Partial asphyxia caused cerebral white matter injury,[15,26] whereas acute and profound asphyxia produced basal ganglia and thalamus injury.[27] In this study, abnormal brain MRI findings were associated with poor outcome. We did not, however, evaluate the relationship between outcome and type of brain injury seen on MRI. Further investigation is necessary to confirm the relationship between outcome and type of MRI abnormality.

Limitations and strengths

This study has some limitations. First, the retrospective study design resulted in missing data; 67 cases (22.8%) did not provide outcome data. But whether or not the follow-up rate affected the true incidence of severe disabilities, is unclear.[28,29] A second limitation was the lack of uniformity among techniques for evaluating neurodevelopment. In Japan, methods for assessing neurodevelopment are subject to the individual clinician's practices and institutional policies. Therefore, it is important to establish a standardized protocol for following high-risk infants.

Nevertheless, this study has several strengths. Notably, the response rate was high at 90.7%. In Japan, approximately 50% of neonates are delivered in private clinics. Mothers and newborns suffering from complications are generally transferred to a regional perinatal center, and it is likely that all infants with moderate or severe HIE are treated in NICU. Therefore, the present results accurately describe the current status of infants with HIE in Japan. Additionally, the findings may contribute information that may be useful for prenatal counseling of parents and for cross-national research.

Acknowledgments

The authors gratefully acknowledge Dr Hiroyuki Kidokoro, Dr Toru Kato, Dr Akihisa Okumura and Dr Fumio Hayakawa, who advised on the design of this study. The authors also gratefully acknowledge all staff members in the institutions enrolled in this study. This work was funded by the Japan Society of Perinatal and Neonatal Medicine.

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Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther
DOI: 10.1159/000348771

Received: November 7, 2012
Accepted after revision: February 5, 2013
Published online: April 18, 2013

The Use Of Amniotic Fluid Discordance in the Early Second Trimester to Predict Severe Twin-Twin Transfusion Syndrome

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Key Words
Amniotic fluid discordance · Twin-twin transfusion syndrome · Monochorionic twin · Ultrasound screening · Second trimester

Abstract
Introduction: The appropriate effectiveness of inter-twin amniotic fluid discordance (AFD) in the early second trimester for the prediction of severe twin-twin transfusion syndrome (TTTS) was evaluated. ***Materials and Methods:*** The largest AFD between 16 and 18 weeks' gestation was analyzed in correlation with TTTS development defined by polyhydramnios with a maximum vertical pocket (MVP) ≥8 cm combined with oligohydramnios with a MVP ≤2 cm using the receiver operating characteristics curve. All pregnancies were stratified according to an AFD cutoff, and perinatal outcomes were compared between two groups. ***Results:*** A total of 223 twin monochorionic pregnancies met the inclusion criteria and 20 patients (8.9%) developed TTTS. An AFD ≥4 cm was calculated to be the optimal point of demarcation to predict subsequent TTTS. The sensitivity and specificity of this AFD cutoff for the development of TTTS were 70 and 97%, respectively. An AFD ≥4 cm was associated with a significantly increased risk of the development of TTTS (70 vs. 2.9%; $p < 0.01$). Those pregnancies with AFD tended to deliver at an earlier gestational age and were also significantly associated with intrauterine fetal deaths. ***Discussion:*** The AFD between monochorionic diamniotic twins in the early second trimester may be useful for the prediction of severe TTTS development.

Introduction

Twin-twin transfusion syndrome (TTTS) is the most critical issue in the prenatal management of a monochorionic diamniotic (MCDA) twin pregnancy and it carries a high mortality and morbidity without treatment [1]. Prenatal treatment by fetoscopic laser photocoagulation (FLP) has been shown to improve the prognosis of affected fetuses [2–4]. Therefore, the early prediction and diagnosis of severe TTTS, especially developed in the mid-second trimester, is extremely important. Several ultrasonographic findings, including inter-twin crown-rump length

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discrepancy, nuchal translucency discrepancy, and abnormal Doppler flow of the ductus venosus have been reported as first trimester predictive factors of subsequent TTTS [5–7]. However, it remains unclear whether these parameters are appropriate for its prediction [8–10].

The development of TTTS has been attributed to an imbalanced circulating plasma volume caused by the blood flow from one fetus to the other via placental anastomoses [11]. The change in the renin-angiotensin cascade induced by hypervolemia of the recipient and hypovolemia of the donor exacerbates amniotic fluid discordance [12]. The diagnosis is based on the presence of polyhydramnios of the recipient twin combined with oligohydramnios of the donor twin. Therefore, moderate AFD between MCDA twins, which do not fulfill the criteria of TTTS, could have emerged prior to the development of TTTS, and the finding could serve as a valuable predictor. Previous studies have advocated moderately discordant amniotic fluid in the second trimester as a predictor for the subsequent development of TTTS [7, 13]. However, the cutoff of AFD required to have a high predictive value has not been fully elucidated.

The objective of this study was to validate the appropriate effectiveness of AFD in the early second trimester for the prediction of TTTS.

Materials and Methods

This was a retrospective cohort study performed at two tertiary perinatal care centers in Japan. All women gave written informed consent to participate and the study protocol was approved by the ethical committee of each institution.

A total of 321 MCDAs were included between October 2008 and March 2012. Pregnancies with major congenital anomalies, chromosomal abnormalities, intrauterine fetal death (IUFD) before 15 weeks of gestation, and twin-reversed arterial perfusion were not included. Pregnancies that developed TTTS within 7 days from the first visit to our hospital were also excluded. Maternal and neonatal data from all pregnancies were collected. The diagnosis of monochorionicity was made at the first trimester ultrasound [14] and confirmed postnatally by placental examination. Serial ultrasonographic assessment, including measurement of the maximum vertical pocket (MVP) of each twin and estimated fetal weight (EFW), was performed at intervals of at least 2 weeks after 16 weeks' gestation. The AFD was calculated by subtracting the smaller MVP from the larger MVP between 16 and 18 weeks' gestation. If there was more than one AFD measurement between 16 and 18 weeks' gestation, the largest AFD before the onset of TTTS was adopted as a predictor.

The diagnosis of TTTS was made by the presence of polyhydramnios with an MVP ≥8 cm combined with oligohydramnios with an MVP ≤2 cm [2]. FLP was offered when the criteria of TTTS were met before 26 weeks' gestation. Delivery was typically planned at 37–38 weeks' gestation, absent any fetal or maternal complications.

Table 1. Maternal baseline characteristics and ultrasonographic parameters

Maternal baseline characteristics	
Maternal age, years	30.7±5.0
Nulliparity	128 (57)
ART	20 (8.9)
Ultrasonographic parameters	
Gestational age at the examination, weeks	17 (16–18)
AFD, cm	0.8 (0–7.3)
EFW of the larger fetus, g	175 (79–305)
EFW of the smaller fetus, g	145 (52–275)
EFW discordant rate >0.25	37 (16)

Data are given as means ± SD, median (range), or n (%). ART = Assisted reproductive technology.

All statistical analyses were performed using a statistical software package (Windows version 17.0; SPSS, Chicago, Ill., USA). We performed univariate analysis of the relationship between AFD, gestational age at the examination, discordant rate of EFW, and the development of TTTS using logistic regression analysis. Subsequently, multiple logistic regression analysis was performed. The discordant rate of EFW was calculated by: (larger EFW – smaller EFW)/larger EFW. We constructed a receiver operating characteristics (ROC) curve to assess AFD as a predictor of subsequent TTTS. The optimal cutoff was calculated using the Youden index. All pregnancies were stratified according to an AFD cutoff. Thereafter, maternal characteristics and perinatal outcomes, including TTTS, were compared between groups. Based on the normality of the data assessed by the Shapiro-Wilk W test, continuous variables were evaluated with a Student's t or Mann-Whitney U test. Nominal variables were evaluated with Fisher's exact test. A $p < 0.05$ was considered statistically significant.

Results

Fifty women referred to our clinic after 19 weeks of gestation were excluded; 5 cases with major congenital anomalies, 4 cases with a twin-reversed arterial perfusion sequence, 9 cases of IUFD before 15 weeks of gestation, 2 spontaneous abortions, and 1 artificial abortion were also excluded. There were 3 cases that developed TTTS within 7 days from the first visit to our hospital, and these cases were also excluded. A total of 223 from 247 women who met the inclusion criteria were included in the study, as 24 women were excluded due to the absence of amniotic fluid volume data.

Maternal baseline characteristics and ultrasonographic parameters are presented in table 1. The median AFD of the 223 twins was 0.8 cm (range: 0–7.3). Twenty pa-

Table 2. Crude and adjusted OR estimated by logistic regression analysis for GA of ultrasonographic scan, EFW discordance, and AFD

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
GA at examination	0.87 (0.49–1.54)	0.63	–	–
EFW discordant rate >0.25	3.10 (1.14–8.41)	0.02	0.54 (0.12–2.30)	0.40
AFD	2.34 (1.75–3.12)	<0.01	2.34 (1.75–3.12)	<0.01

GA = Gestational age.

tients (8.9%) developed TTTS and one of them opted for a pregnancy termination following the diagnosis of TTTS. The median gestational age of TTTS onset was 19 weeks' gestation (range: 17–35). Although spontaneous IUFDs occurred in 11 cases (2.4%), there were no cases with demise of both fetuses.

With univariate analysis, there was a significant correlation between AFD and the development of TTTS (OR: 2.34; 95% CI: 1.75–3.12; $p < 0.01$); however, there was no correlation between gestational age at the examination and TTTS (OR: 0.87; 95% CI: 0.49–1.54; $p = 0.63$). The prevalence of cases with a discordant rate >0.25 was also significantly higher in the TTTS group by the analysis with a χ^2 test (OR: 3.10; 95% CI: 1.14–8.41; $p = 0.02$). After multiple logistic regression analysis, the only significant variable that remained was AFD (adjusted OR: 2.34; 95% CI: 1.75–3.12; $p < 0.01$; table 2).

The ROC curve of AFD in relation to the occurrence of TTTS was constructed (fig. 1). The area under the ROC curve was 0.77 and the 90th percentile of AFD (3.95 cm) appeared to be an optimal point of demarcation to predict subsequent TTTS. The sensitivity and specificity of this AFD cutoff for the development of TTTS were 70 and 97%, respectively. AFD was evaluated to the first decimal place, and an AFD ≥4 cm was used to assess the relation between this cutoff and other maternal characteristics and pregnancy outcomes.

After stratification of the study group by an AFD ≥4 cm, no differences in maternal age, the prevalence of nulliparity, or conception via assisted reproductive therapy were present. In the group with AFD ≥4 cm, the median MVP of the recipient and donor fetus were 7.0 (range: 4–8.9) and 1.3 (range: 0–4.9), respectively.

An AFD ≥4 cm was associated with a significantly increased risk of developing TTTS (70 vs. 2.9%; $p < 0.01$). Cases of TTTS occurring before 26 weeks' gestation, which made them candidates for FLP, were significantly greater in the group with an AFD ≥4 cm (table 3). Other adverse outcomes were more frequent in twins with an AFD ≥4 cm. Pregnancies with an AFD in this range tended to be delivered at an earlier gestational age and IUFD was significantly more likely to occur in twins with an AFD ≥4 cm. Four of 5 IUFD cases in the group with an AFD ≥4 cm occurred after FLP was performed for TTTS. The accuracy of an AFD ≥4 cm as a predictor of TTTS is presented in table 4.

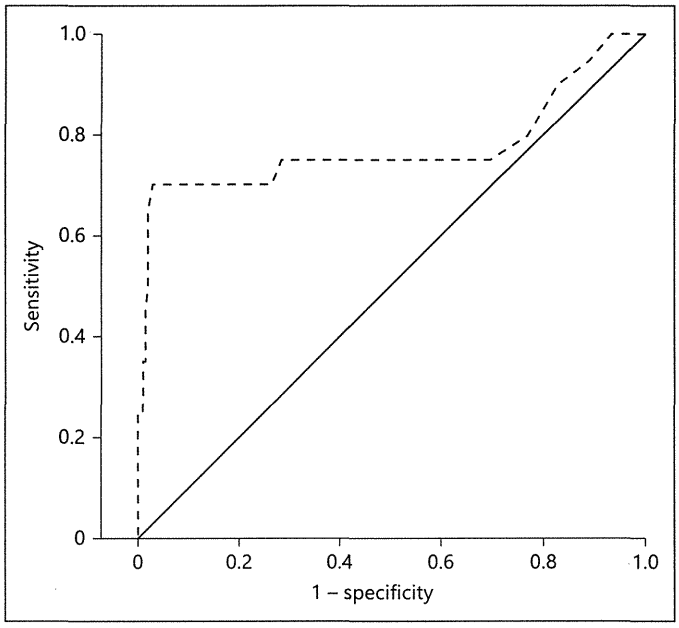

Fig. 1. ROC curve for inter-twin AFD for prediction of the development of TTTS.

Discussion

This study found that MCDA twins presenting with moderate AFD in the early second trimester are a high-risk group for the development of TTTS. The findings of this series demonstrate that AFD in the early second tri-

Table 3. Pregnancy outcomes stratified by AFD ≥4 cm

Outcome	AFD ≥4 cm (n = 20)	AFD <4 cm (n = 203)	p
Gestational age at delivery, weeks	35 (25–40)	37 (27–40)	<0.01
Delivery at <34 weeks	7/19 (36)	25/203 (12)	0.01
TTTS	14 (70)	6 (2.9)	<0.01
TTTS <26 weeks	13 (65)	4 (1.9)	<0.01
Onset of TTTS, weeks	18 (17–27)	23 (20–35)	<0.01
TOP	1 (5)	0 (0)	0.15
IUFD	5/38 (13)	6/406 (1.4)	<0.01

Values are given as the median (range) or n (%). TOP = Termination of pregnancy.

Table 4. Accuracy of AFD ≥4 cm as a predictor of TTTS

	Sensitivity	Specificity	PPV	NPV	RR (95% CI)
TTTS	70	97	70	97	23.6 (10.2–54.7)
TTTS <26 weeks	65	98	76	96	22.5 (10.3–48.8)

Values are percentages unless otherwise indicated. PPV = Positive predictive value; NPV = negative predictive value; RR = relative risk.

mester detected 70% of subsequent TTTS in MCDA twin pregnancies, compared with only 2.9% in the low-risk group.

The prevalence of TTTS was estimated to be 8% among monochorionic twins [15, 16], and it is associated with high perinatal mortality and morbidity [1, 17, 18]. FLP markedly improves the prognosis of twins with TTTS in the mid-second trimester [2–4, 19]; therefore, it is important to identify patients who should be treated with FLP in a timely manner. Additionally, some degree of discrepancy in amniotic fluid volume may indicate the onset of an imbalance of circulating plasma volume via placental anastomoses. Therefore, we considered moderate AFD in MCDA twins during the early second trimester as a predictor of TTTS and MCDA twins with moderate AFD to be at a high risk of developing TTTS. We did not include the cases that developed TTTS within 7 days from the first visit to our hospital; this was done to exclude previously existing TTTS at the time of assessment.

Lewi et al. [7] demonstrated that pregnancies with moderate AFD at 16 weeks of gestation were more likely to develop TTTS with a sensitivity of 67% and a positive predictive value of 40%, even though the predictive value of assessment at this period was not necessarily high. Furthermore, the degree of AFD judged 'moderate' was not defined. Therefore, we used an AFD ≥4 cm between 16 and 18 weeks of gestation to identify the group at risk for TTTS on the basis of ROC analysis. With high specificity (97%) and a high negative predictive value (97%), this appears to be a cutoff that has a relatively high predictive value and indicates that it may be valuable both for identifying MCDA twin pregnancies that will not develop TTTS and for patient counseling. Once an increase of AFD above 4 cm was observed, a shortening of the interval of ultrasonographic assessment or a referral to the tertiary care center providing FLP for TTTS should be considered. In cases of twins that developed TTTS before 26 weeks' gestation, and whose mothers were offered to perform FLP, similar predictive values were derived. The association between moderate AFD in the early second trimester and the development of TTTS was previously described by Van Mieghem et al. [13]. Using an AFD ≥3.1 cm before 20 weeks' gestation as the predictor, sensitivity and specificity for the development of TTTS were 77 and 91%, respectively. Despite the fact that the significance of the cutoff value has been debated, these predictive values were quite similar to the findings of our study.

TTTS appeared to influence the prevalence of both preterm delivery at <34 weeks' gestation and IUFD in the group of AFD ≥4 cm. Five of 7 pregnancies that were delivered before 34 weeks' gestation in the group of

AFD ≥4 cm developed TTTS. Spontaneous preterm delivery occurred in 4 cases after FLP, and in another case urgent delivery was performed because of TTTS onset at 27 weeks' gestation. In 5 cases with IUFD, 4 fetal deaths were also related to TTTS and another case was complicated by severe fetal growth restriction.

There may be some limitations to this study. First, because it had a retrospective cohort design, some cases were excluded due to insufficient amniotic fluid volume data. The excluded population, in which there were no cases with TTTS, was not large; thus, these exclusions appeared to have a little impact on the prediction of TTTS. Second, only AFD was analyzed as a predictive factor for TTTS development in this study. About half of TTTS pregnancies are accompanied by abnormal Doppler flow in the umbilical artery, ductus venosus, or umbilical vein [20]. Therefore, a different predictive value of AFD for TTTS may be obtained when fetal Doppler parameters are included in the analysis. In view of this, a prospective cohort study should be considered.

In conclusion, the AFD between MCDA twins in the early second trimester is useful for predicting severe TTTS development. This study provides valuable information that can be used for counseling and stratification of pregnancy follow-up.

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Novel Insights from Clinical Practice

Fetal Diagnosis and Therapy

Fetal Diagn Ther
DOI: 10.1159/000354985

Received: May 21, 2013
Accepted after revision: August 8, 2013
Published online: September 14, 2013

Therapy by Laser Equatorial Placental Dichorionization for Early-Onset Spontaneous Twin Anemia-Polycythemia Sequence

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Established Facts

- While twin anemia-polycythemia sequence (TAPS), caused by inter-twin blood shunting via miniscule arteriovenous anastomoses, is occasionally related to adverse outcomes, the optimal perinatal management for TAPS remains unclear.
- Concerns exist regarding the technical difficulty of laser therapy as a curative treatment.

Novel Insights

- Laser therapy using equatorial placental dichorionization could be a viable approach for TAPS, even if undetectable vascular anastomoses are present.

Key Words
Monochorionic twin · Twin anemia-polycythemia sequence · Laser therapy · Intrauterine transfusion · Fetal anemia

Abstract
We report a case of twin anemia-polycythemia sequence (TAPS) treated by fetoscopic laser equatorial placental dichorionization, also known as the 'Solomon technique', at 24 weeks of gestation. TAPS was present despite the absence of fetoscopically visualized chorionic anastomoses from the donor to the recipient twin. The goal of this procedure was to prevent post-laser TAPS in cases of twin-twin transfusion syndrome. The surgery and subsequent intrauterine blood transfusion to the donor twin could result in the survival of both twins without hematologic or neurological complications. Following the surgery, a placental injection test revealed no residual anastomoses. At present, laser therapy is not always feasible for TAPS, primarily because of its difficulty. However, laser therapy using the Solomon technique could be a viable approach for early-onset TAPS, especially in difficult situations in which undetectable vascular anastomoses related to TAPS are present.

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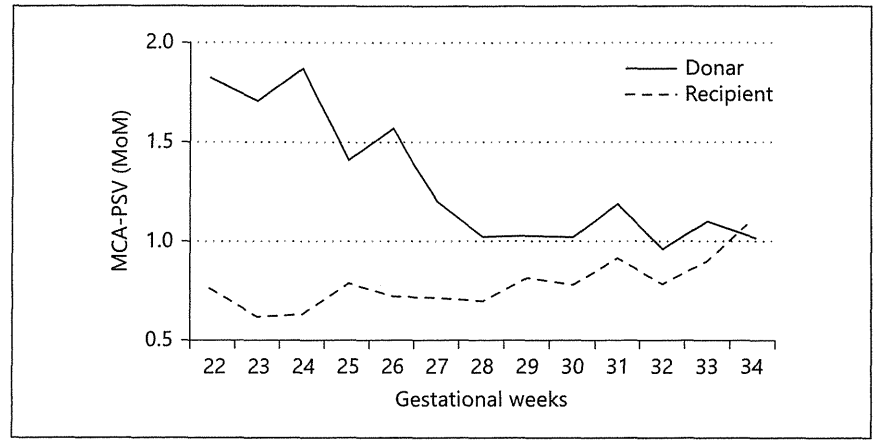

Fig. 1. MCA-PSV of the donor and the recipient twin from 22 weeks of gestation onward, MoM [1].

Case Report

A 27-year-old nulliparous woman with a monochorionic diamniotic twin gestation conceived via in vitro fertilization; she had been managed at our center from the first trimester onward. Ultrasonography at 18 weeks of gestation revealed that the middle cerebral artery peak systolic velocity (MCA-PSV) in one twin was elevated to 1.57 multiples of median (MoM) [1], while that of the other twin was decreased to 0.87 MoM. Because the discordance in MCA-PSV persisted in the absence of amniotic fluid discordance under expectant management, the patient was diagnosed with twin anemia-polycythemia sequence (TAPS) at 20 weeks [2]. Concurrently, the discordance of echogenicity of the placenta was also noted; high echogenicity and enlargement in the donor twin and relative hypoechogenicity in the recipient twin were noted. The donor twin was found to have tricuspid as well as mitral regurgitation at 22 weeks; however, there were no hydropic signs. The patient was classified as TAPS stage 2 at 23 weeks, when the MCA-PSV was 1.71 MoM in the recipient twin and 0.62 MoM in the donor twin.

At 23 weeks, percutaneous umbilical blood sampling, which was performed to confirm the exact value of fetal hemoglobin (Hgb) and the hematocrit (Hct), indicated that the Hgb and Hct levels were 16.3 g/dl and 48.8% in the recipient twin and 5.6 g/dl and 18.8% in the donor twin, respectively. The reticulocyte count ratio was elevated to 3.4 in the donor twin. Fetoscopic laser photocoagulation (FLP) for TAPS with a posterior placenta was performed at 24 weeks and 1 day of gestation under epidural anesthesia. The patient provided written informed consent and the hospital's institutional review board approved all study protocols. Subsequent to an amnioinfusion of 1,600 ml warmed normal saline, fetoscopy revealed 2 small arteriovenous (AV) anastomoses from the recipient to the donor twin, which were ablated by laser. However, AV anastomoses from the donor to the recipient twin as well as superficial vascular anastomoses including arterio-arterial or venovenous anastomoses were not identified fetoscopically. On the assumption of the existence of miniscule AV anastomoses from the donor to the recipient twin, a line was drawn with the laser that connected the dots, which had been coagulated, from end to end on the placenta. The surgery time was 50 min and there were no surgical complications.

FLP was followed by an intrauterine blood transfusion for the donor twin, whose Hgb level was 3.8 g/dl 1 day postoperatively. The MCA-PSV in the donor twin normalized immediately after the procedure; however, it took several weeks for the MCA-PSV of the recipient twin to return to the normal range. In the third trimester, the MCA-PSV of both twins remained normal (fig. 1), and the echogenicity of the placenta became uniform. The twins were delivered by elective cesarean section; the indication was twin gestation at gestational week 38. The recipient twin weighed 2,778 g and the Apgar scores were 8/9, while the donor twin weighed 2,524 g and the Apgar scores were 8/9. Hgb and Hct values in umbilical venous blood at birth were 15.9 g/dl and 48.0% in the recipient twin and 12.5 g/dl and 41.8% in the donor twin, respectively. The donor twin was managed in the neonatal intensive care unit for transient tachypnea and hypoglycemia until normal brain magnetic resonance imaging was confirmed at age 20 days. There were no obvious neurological abnormalities imaged with brain ultrasonography in either twin at 30 days of age. A patent placental vascular anastomosis could not be recognized with a dye injection test of the chorionic vessels (fig. 2).

Discussion

Approximately 2–6% of monochorionic twin pregnancies develop spontaneous TAPS [3, 4]. The major cause is thought to be the shunting of blood from the donor to the recipient twin via miniscule chorionic AV anastomoses; this can result in severe anemia and hypoalbuminemia in the donor twin and polycythemia and thrombocytopenia in the recipient twin [5–7]. Although the actual perinatal mortality and morbidity rate has not been fully demonstrated, twins with TAPS can occasionally be affected by perinatal death or neurological morbidities [8, 9]. Further studies are required to establish the optimal management strategy. The efficacy of an intra-